REMARKS

Prior to entry of the present amendments, claims 8, 9, 13, 14, 23 and 24 were pending. Claims 28 to 33 have been added herein. Thus, claims 8, 9, 13, 14, 23, 24, and 28 to 33 are pending and presently under examination.

Regarding the new claims

Claims 28 to 33 have been added herein, Claims 28, 30 and 32 have all the limitations of claims 8, 13 and 23, respectively, and further indicate that the recited antimicrobial peptide has an amphipathic α-helical structure. The further limitation in claims 28, 30 and 32 is supported throughout the specification, for example, at page 18, lines 1-4, which indicates that antimicrobial peptides can share an amphipathic α-helical structure. New dependent claims 29, 31 and 33 indicate that the recited antimicrobial peptide having an amphipathic α-helical structure includes the sequence $_D$(KLAKLAK)$_2$. New claims 29, 31 and 33 are supported throughout the specification, for example, at page 17, lines 3-14, which discloses the structure of exemplary antimicrobial peptides with an amphipathic α-helical structure including the sequence $_D$(KLAKLAK)$_2$.

As set forth above, each of the new claims is supported by the specification as filed and does not add new matter. Applicants therefore respectfully request that the Examiner enter the new claims.

Regarding the rejections

Regarding the written description rejection

The objection to the specification and corresponding rejection of claims 8, 9, 13, 14, 23 and 24 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description, are respectfully traversed. The Office Action asserts that the specification lacks sufficient written description for the genus of antimicrobial peptides "having low mammalian cell toxicity when not linked to said prostate-homing peptide." The Office Action asserts that the specification must provide sufficient distinguishing identifying characteristics for this genus and notes that factors to be considered in regard to written description are the disclosure of complete or partial

structure, physical or chemical properties and functional characteristics, structure/function correlations and methods of making the peptides.

Further in this regard, the Office Action asserts that the only written description provided in this case, a functional description of the recited antimicrobial peptides, does not satisfy the written description requirement. The Office Action emphasizes that required structural elements have not been disclosed. It is further alleged that the specification teaches that some naturally occurring antimicrobial peptides such as mellitin are toxic to mammalian cells, while others such as the magainins and cecropins have low mammalian cell toxicity when not linked to a homing peptide.

Applicants submit that the specification provides sufficient written description for the recited genus of antimicrobial peptides having low mammalian cell toxicity. In particular, Applicants submit that the genus of antimicrobial peptides having low mammalian cell toxicity has been clearly described in regard to its functional characteristics, and, as discussed further below, written description of structural characteristics common to such antimicrobial peptides also is provided in the specification.

The specification provides written description regarding functional characteristics of the recited genus of antimicrobial peptides having low mammalian cell toxicity by teaching that an antimicrobial peptide incorporated into a pro-apoptotic conjugate of the invention has low mammalian cell toxicity when not linked to a homing molecule and that mammalian cell toxicity can be assessed by routine methods (page 16, lines 1-8). In particular, the specification teaches that an antimicrobial peptide having "low mammalian cell toxicity" is not lytic to human erythrocytes or requires concentrations of greater than 100 μM for lytic activity (page 16, lines 8-12). As taught in the specification, mammalian cell toxicity can be assayed by routine methods such as *in vitro* lysis of human erythrocytes as described in Javadpour et al. (page 16, lines 1-8). Applicants respectfully point out that, in view of the guidance in the specification, one skilled in the art readily would have been able to determine which proteins are lytic to human erythrocytes and, therefore, not encompassed within the recited genus of antimicrobial peptides having low mammalian cell toxicity when not linked to a prostate-homing peptide. In sum, written

description regarding functional characteristics of the recited genus of antimicrobial peptides having low mammalian cell toxicity is clearly provided in the specification.

As additional written description, the specification describes structural characteristics common to many antimicrobial peptides. Firstly, the specification teaches that an antimicrobial peptide typically is highly basic (page 15, lines 3-4). Secondly, the specification teaches that an antimicrobial peptide can have, for example, an amphipathic α-helical structure and that an amphipathic α-helical structure is a common feature of many antimicrobial peptides (page 15, lines 4-8; page 18, lines 1-29). An antimicrobial peptide also can have the structure of a β-strand/sheet-forming peptide (specification at page 15, lines 3-11). In addition, the specification provides further written description for the structural characterization of amphipathic α-helical peptides by teaching that an amphipathic α-helical peptide useful in the invention can have at least about 20% helicity when assayed in amphipathic media and that the percentage of α-helicity can be determined by routine methods, for example, by measuring molar ellipticity at 222 nm as described in Javadpour et al. and McLean et al (page 19, lines 19-32). In sum, in addition to providing written description for functional characteristics of the recited genus of antimicrobial peptides having low mammalian cell toxicity when not linked to a prostate-homing peptide, the specification provides written description for structural characteristics common to many such antimicrobial peptides.

As further guidance regarding members of the genus of antimicrobial peptides having an α-helical structure , the specification provides the structure of exemplary synthetic peptides such as peptides having the formula $[(X_1X_2X_2)(X_1X_2X_2)X_1]_n$ (SEQ ID NO: 205) or $[(X_1X_2X_2)X_1(X_1X_2X_2)]_n$ (SEQ ID NO: 206), where X_1 is a polar residue, X_2 is a nonpolar residue, and n is 2 or 3; and peptides having the sequence $(KLAKLAK)_2$ (SEQ ID NO: 200); $(KLAKKLA)_2$ (SEQ ID NO: 201); $(KAAKKAA)_2$ (SEQ ID NO: 202); or $KLGKKLG)_3$ (SEQ ID NO: 203). Applicants submit that the written description in the specification regarding functional and structural characteristics of the recited genus of antimicrobial peptides having low mammalian cell toxicity in combination with the description of the structure of exemplary species of the genus is sufficient to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the priority application was filed.

Regarding Javadpour et al.

According to the Office Action, Javadpour et al. report that, of the synthetic peptides shown in Table 2, only $(KLGKKLG)_3$ has the required low toxicity to mammalian cells. Applicants respectfully disagree. Rather, Javadpour describe a structure/function correlation, emphasizing structural and functional similarities between $(KLGKKLG)_3$ and alanine-containing 14-mers such as $(KLAKKLA)_2$ and $(KLAKLAK)_2$. Specifically, Javadpour et al. conclude that "[t]he propensity to α-helical conformation of the peptides in amphipathic media is proportional to their 3T3 cytotoxicity" (page 3107, last sentence of abstract). Analyzing their data shown in Table 2, Javadpour et al. conclude that molar helicity of the peptides is correlated to the chain length of the peptides and that alanine-containing peptides of the same length have a similar helical content while analogous glycine-containing peptides have a lower helical contact. Notably, the helical contact of $(KLGKKLG)_3$ and the alanine-containing 14-mers $(KLAKKLA)_2$ and $(KLAKLAK)_2$ are similar, in the range of 24-37% helicity (see Javadpour et al. at page 3109, second column, first full paragraph). In regard to mammalian cell cytotoxicity, Javadpour et al. conclude that both the alanine-containing 14-mer peptides and $(KLGKKLG)_{2,3}$ peptides are less cytotoxic than magainin 2 amide and cecropin B amide (page 3112, last paragraph of discussion). Again, Javadpour et al. find a structure/function correlation between helicity and mammalian cytotoxicity (last sentence of abstract); this conclusion is consistent with the written description in the specification teaching that amphipathic α-helical peptides useful in the invention can have at least about 20% helicity.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and remove the written description rejection of claims 8, 9, 13, 14, 23 and 24 under the first paragraph of 35 U.S.C. § 112.

Regarding the enablement rejection

The objection to the specification and corresponding rejection of claims 9, 14 and 24 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, are respectfully traversed. Claims 9, 14 and 24 are directed to methods which rely on a prostate-homing peptide that includes the sequence SMSIARL (SEQ ID NO: 207) or a functionally equivalent sequence. While the Office Action acknowledges that the specification enables the use of peptide SEQ ID

NO: 207, it is alleged that the specification fails to provide enablement for a sequence which is "functionally equivalent" to SEQ ID NO: 207.

The Office Action bases the enablement rejection on the definition of "functionally equivalent sequence," which states, in part, that a functionally equivalent sequence functions similarly in that the sequence binds selectively to the same receptor. Given that the specification does not teach which receptor binds peptide SMSIARL (SEQ ID NO: 207), the Office Action concludes that one skilled in the art would not have been able to perform an assay to determine whether a peptide were "functionally equivalent" to SEQ ID NO: 207.

Applicants respectfully traverse the enablement rejection of claims 9, 14 and 24, submitting that, in view of the specification, one skilled in the art would have been able to practice the full scope of the invention without undue experimentation. In particular, the specification provides guidance regarding how to make and use a "functionally equivalent sequence" by teaching that a functionally equivalent sequence binds to the endothelium of prostatic blood vessels as does peptide SEQ ID NO: 207 and, furthermore, binds selectively to the same receptor as does SMSIARL (SEQ ID NO: 207; page 78, lines 4-10). In addition, the specification provides guidance regarding assays suitable for identifying peptides which are functional equivalents of SEQ ID NO: 207. Firstly, in regard to selective binding to prostate blood vessels, the specification teaches, for example, that phage displaying a homing peptide can be localized, for example, by staining with anti-M13 (phage) antibodies (page 97, lines 6-22). The specification also exemplifies, for example, peroxidase staining of human prostate tissue following injection of SMSIARL (SEQ ID NO: 207)-phage and incubation of tissue sections with anti-phage antibody (page 8, line 27, to page 9, line 8; page 107, Example IXE). Thus, the specification provides guidance regarding routine assays for confirming that a "functionally equivalent sequence" binds prostatic blood vessels as does SEQ ID NO: 207.

Secondly, guidance is provided in the specification regarding assays suitable for confirming selective binding to the receptor which binds SEQ ID NO: 207. Specifically, in view of the teachings of the specification, one skilled in the art would have been able to use routine competition assays to observe selective binding of a "functionally equivalent sequence" to the receptor which binds peptide SEQ ID NO: 207. Notably, such competition assays do not require

isolation or identification of the receptor which binds peptide SEQ ID NO: 207. As guidance to the skilled person in regard to such competition assays, the specification teaches, for example, that the failure of a first peptide to competitively inhibit homing of a second peptide indicates that the two peptides bind different receptor sites. For example, the specification teaches that a synthetic NGR-containing peptide, CNGRC (SEQ ID NO: 8), inhibited homing when co-injected with phage expressing CNGRCVSGCAGRC (SEQ ID NO: 3), NGRAHA (SEQ ID NO: 6) or CVLNGRMEC (SEQ ID NO: 7) but did not inhibit homing of phage expressing peptide CDCRGDCFC (SEQ ID NO: 1), even when administered in excess, indicating that NGR-containing peptides and RGD-containing peptides bind to different receptor sites (page 31, line 18, to page 2, line 5). Thus, in view of the specification and even in the absence of an identified or isolated receptor, one skilled in the art would have known that routine competition assays can serve to corroborate whether a peptide binds to the same receptor as peptide SEQ ID NO: 207 and, therefore, whether a peptide has a sequence which is a functional equivalent of SEQ ID NO: 207.

In view of the above remarks, it is clear that only routine work, and not undue experimentation, would have been required for one skilled in the art to practice the claimed invention with a sequence is a functional equivalent of SEQ ID NO: 207. Accordingly, the Examiner is respectfully requested to reconsider and remove the enablement rejection of claims 9, 14 and 24 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance, and that a notice be issued to that effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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